PATENT COOPERATION TREATY 18 FEB 2005

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	16.02.2005
Applicant's or agent's file reference: 2003.796 WO	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/051357	05.07.2004	10.07.2003

Applicant: AKZO NOBEL N.V. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Ullrich, J Tel. +49 89 2399-8048

Form PCT/IPEA/416 (January 2004)

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 2003.796 WO	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/051357	International filing date *(day/month/year)* 05.07.2004	Priority date *(day/month/year)* 10.07.2003
International Patent Classification (IPC) or national classification and IPC C07D401/04, C07D471/14		
Applicant AKZO NOBEL N.V. et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
30.12.2004	16.02.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Guspanova, J Telephone No. +49 89 2399-7834

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-10 as originally filed

   Claims, Numbers

   1-10 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

   * *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10
	No:	Claims	
Inventive step (IS)	Yes:	Claims	9
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. **Relevant documents**

The following documents **D1-D3** are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: US-A-4 062 848 (VAN DER BURG WILLEM JACOB) 13 December 1977 (1977-12-13)

D2: WO 00 62782 A (SINGER CLAUDE ;TEVA PHARMA (IL); LIBERMAN ANITA (IL); FINKELSTEIN) 26 October 2000 (2000-10-26)

D3: SELDITZ U ET AL: 'Direct enantiomeric separation of mianserin and 6-azamianserin derivatives using chiral stationary phases' JOURNAL OF CHROMATOGRAPHY A, ELSEVIER SCIENCE, NL, vol. 803, no. 1-2, 17 April 1998 (1998-04-17), pages 169-177, XP004117830 ISSN: 0021-9673

2. **Novelty**

The present application claims an one-step process for the preparation of enantiomerically pure mirtazapine of formula (I) comprising ring closure of a compound of general formula (II) with enantiomeric excess by treatment with a suitable acid (claims 1-9). A method for the selection of an acid or an acid/solvent combination suitable for the process of claim 1 is also claimed (claim 10). This process is in general defined by the same technical features as the process of the present claim 1.

Prior art D1 discloses a ring closure process for the preparation of racemic mirtazapine (Examples I and IV) followed by an optical resolution of mirtazapine using (-)O,O-dibenzoyltartaric acid (Example XIX).

D2 discloses a ring closure process for the preparation of racemic mirtazapine starting with racemic compounds of formula IV which corresponds with the formula (II) of the present application.

D3 discloses an optical resolution of mirtazapine (6-azamianserin; formula 2) using Chiralpak AD column (Table 3).

Since none of the prior art documents D1-D3 discloses the starting compounds of formula (II) with enantiomeric excess, the subject-matter of the present claims 1-10 appears novel in view of D1-D3, according to Article 54(1) and (2) EPC.

2. **Inventive step**

The problem underlying the present application is seen in the provision of an improved process for the preparation of enantiomerically pure mirtazapine of formula (I).

The closest prior art represented by D1 discloses a two-steps process comprising

1. a ring closure of racemic compounds of formula II (Example I.4 and IV.) which corresponds with the formula (II) of the present application and
2. a resolution of racemic mirtazapine obtained in the first step with O,O-dibenzoyltartaric acid (Example XIX).

The difference between D1 process and that of the present application resides in that the starting compounds used in the present process are present in an enantiomeric excess and not in a racemic form.

The solution to the problem stated above is seen in the provision of the process described in the present claim 1, in which process the starting compounds of formula II are used in an enantiomeric excess and not in the racemic form. The starting material is treated with a "suitable" acid in the absence of a solvent or a "suitable" combination of an acid and an organic solvent. Such a solution seems to be obvious to the person skilled in the art in view of document D1 from following reasons:
D1 explicitly suggests using optically active compound of formula II instead of the corresponding racemic starting material (column 6, lines 53-59). The skilled person would first try to perform the synthesis with the acid used in Example I, step 4. or in Example IV of D1, where the preparation of mirtazapine is described. Then the skilled person would try to use different types of acids in order to find out, which acid would be "suitable" for the reaction in order to avoid excessive racemisation during the reaction and to achieve highest possible enantiomeric excess of the product, optically active mirtazapine. The list

of possible acids is given in column 2, lines 1-17 of D1. To select a "suitable" acid from the list of acids useful for dehydration given in column 2 and to use it in the absence of a solvent according to Examples I.4 and IV of D1 seems to be a common practice of the skilled person seeking the optimal reaction conditions. Therefore, the teaching of D1 would obviously lead the person skilled in the art to the subject-matter presently claimed in claim 1.
Thus, the subject-matter of the present claim 1 is considered not-involving an inventive step, according to Article 56 EPC.

The dependent process claims 2-4 are also considered not involving inventive step, since the additional technical features described therein are known or suggested in the art by documents D1 and D2.

Claim 2: Using a suitable acid in the absence of a solvent is known from D1 (Examples I.4. and IV, list of acids in column 2) and D2 (Examples 1-3, page 6, lines 12-23).

Claim 3: Using a protic acid is also known from D1 and D2 (use of conc. H_2SO_4 in the same Examples as stated above).

Claim 4: Use of polyphosphoric acid is suggested by the both prior art documents D1 (column 2, paragraph 1 and 2) and D2 (claim 3).

The dependent process claim 5 defines particularly the ratio between polyphosphoric acid and the compound of formula (II). Although definition of a such a ratio has not been found in the cited prior art, the skilled person seeking for the optimal reaction conditions would try to find the best ratio between polyphosphoric acid and the compound of formula (II). An optimization of a reaction conditions in the said way is regarded as an every day practice of a person skilled in the art. Since it has not been shown in the present application, that the ratio 5:1 claimed in the present claim 5 leads to a better results then a reaction in which the said ratio is different from 5:1, an inventive step of the present claim 5 cannot be acknowledged.

The dependent process claims 6-9 introduce a novel technical feature in the process of the present claim 1, namely the use of a suitable acid and an organic solvent in combination. The subject-matter of the said claims could be considered as involving an inventive step, when certain improvement of the present process over the prior art processes can be

seen. Such an improvement can be seen in a high enantiomeric excess achieved when a certain combination of acid with a solvent has been used in the reaction. It is indeed demonstrated by the present Examples 1-3, in which the reaction yields of 68-72% are comparable with the yields of the Examples given in D1 (Example I.4 and IV) and D2 (Examples 2 and 3) and a high enantiomeric excess 99,2-99,7% is achieved. However, it has also been noted that not every organic solvent used in the ring closure leads to a higher enantiomeric excess of optically active mirtazapine. E.g. the present Example 9 and comparative Example 10 in which ethanol and dichloromethane, respectively are used as a solvent provide (S)-mirtazapine in yields 59% and 62%, respectively with a low enantiomeric excess (62%; 36%) as a result of a large degree of racemisation during the reaction. Since the process claims 6-8 comprise organic solvents, which solvents (e.g. ethanol or dichloromethane) do not improve the yield of the ring closure step, they are considered not inventive.

The present claim 10 does not involve an inventive step from the following reasons:

The subject-matter of claim 10 is a method for the selection of an acid or an acid/solvent combination suitable for the process of claim 1. It is in general defined by the same technical features as the process of the present claim 1. Additionally, it comprises determining a loss of enantiomeric excess by the reaction and identifying an acid or acid/solvent combination. The said method for the selection is considered obvious for the person skilled in the art, because skilled person knowing the fact that not every acid is suitable for the reaction of claim 1 would try to identify the best acid or acid/solvent combination while detecting the changes in the reaction conditions, as it is the common practice of the skilled person optimising the reaction concerned.

Having regard to what has been stated above, solely the process claim 9 which specify the solvent used as being *N*-methylpyrrolidinone or DMF does involve an inventive step, according to Article 56 EPC.

Re Item VIII

Certain observations on the international application

The following inconsistency between the description and the claims according to Article 6 PCT has been found in the present application. According to the description on page 4, lines 29-31 and on page 5, paragraph 2, some of the combinations of acid/solvent are not

suitable for the process presently claimed. However, such statements are not involved in the present claims. The said inconsistency throws doubt on the extent of the protection south for the present application.

It is to be mentioned that the term "suitable acid" used in the present claims defines an acid by its desired function, contrary to the requirements of support in the sense of Article 5 and 6 PCT. The fact that any acid could be selected and checked does not overcome this objection, as the skilled person would not have knowledge beforehand as to whether it would fall within the scope claimed. Undue experimentation would be required to randomly select acids suitable for the reaction claimed.